Lineage- and developmental stage-specific mechanomodulation of induced pluripotent stem cell differentiation.

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Authors: Maricela Maldonado, Rebeccah J Luu, Gerardo Ico, Alex Ospina, Danielle Myung, Hung Ping Shih, Jin Nam

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Public Summary:
To maximize the translational utility of human induced pluripotent stem cells (iPSCs), the ability to precisely modulate the differentiation of iPSCs to target phenotypes is critical. Although the effects of the physical cell niche on stem cell differentiation are well documented, current approaches to direct step-wise differentiation of iPSCs have been typically limited to the optimization of soluble factors. In this regard, we investigated how temporally varied substrate stiffness affects the step-wise differentiation of iPSCs towards various lineages/phenotypes

Scientific Abstract:
BACKGROUND: To maximize the translational utility of human induced pluripotent stem cells (iPSCs), the ability to precisely modulate the differentiation of iPSCs to target phenotypes is critical. Although the effects of the physical cell niche on stem cell differentiation are well documented, current approaches to direct step-wise differentiation of iPSCs have been typically limited to the optimization of soluble factors. In this regard, we investigated how temporally varied substrate stiffness affects the step-wise differentiation of iPSCs towards various lineages/phenotypes. METHODS: Electrospun nanofibrous substrates with different reduced Young's modulus were utilized to subject cells to different mechanical environments during the differentiation process towards representative phenotypes from each of three germ layer derivatives including motor neuron, pancreatic endoderm, and chondrocyte. Phenotype-specific markers of each lineage/stage were utilized to determine differentiation efficiency by reverse-transcription polymerase chain reaction (RT-PCR) and immunofluorescence imaging for gene and protein expression analysis, respectively. RESULTS: The results presented in this proof-of-concept study are the first to systematically demonstrate the significant role of the temporally varied mechanical microenvironment on the differentiation of stem cells. Our results demonstrate that the process of differentiation from pluripotent cells to functional end-phenotypes is mechanoresponsive in a lineage- and differentiation stage-specific manner. CONCLUSIONS: Lineage/developmental stage-dependent optimization of electrospun substrate stiffness provides a unique opportunity to enhance differentiation efficiency of iPSCs for their facilitated therapeutic applications.